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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/961,381	LYNCH ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-59 and 61-79* is/are pending in the application.

4a) Of the above claim(s) *9-12,20-35,38-58,65-68 and 76-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,13-19,36,37,59,61-64,69-75 and 79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/13/04,4/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments filed April 23, 2004 have been fully considered, but are not persuasive. The amendment has been entered. Claims 1, 3-59, 61-79 are pending.

Newly submitted claim 79 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 79 has an additional step of contacting the cells with amyloid as well as adding a substance and determining the effect of the substance on lysosomal dysfunction, microglia activation or changes in cathespin D content. Thus, this method is patentably distinct from the methods originally presented which did not require contacting the cells with amyloid.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 79 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The amendment filed April 23, 2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, is as follows: The originally filed specification clearly states that TGF is a modulator of integrins. The specification states:

> "The term "condition that modulates integrins or integrin receptors" refers to any condition that might accomplish integrin or integrin receptor modulation. In addition to the compounds referred to in the earlier paragraph, additional examples of modulatory compounds include amyloid beta peptide, oxidative free radicals (OH-, O2-, etc.), lysosomal enzyme inhibitors (chloroquine, N-CBZ-L-phenylalanyl-L-alanine-diazomethylketone, N-CBZ-L-phenylalanyl-L-phenyl-alanine-diazomethylketone, β-amyloid, and mimetics thereof etc.), or inflammatory factors (TGFP, IL-1β, LPS, etc.). These compounds can be used individually or in a cocktail containing a combination of more than one compound or in combination with the above compounds" (specification, page 19, parag. 0065); and
>
> "Examples of modulatory compounds include oxidative free radicals (Fe , H2O2, etc.), lysosomal enzyme inhibitors (chloroquine, N-CBZ-L-phenylalanyl-L-alanine-

> diazomethyketone, N-CBZ-L-phenylalanyl-L-phenylalanine-diazomethylketone, and mimetics thereof etc.), or inflammatory factors (TGFb, IL-1b, LPS, etc.)." (specification, page 38, parag. 0123).

Thus, there is no support for applicant's amendment to the specification, which alters the original disclosure such that those compounds originally stated to be modulators of integrins are only compounds to be used with modulators. This alteration presents a material change to the specification, which is not permissible.

Applicant argues that the artisan would recognize that the list of modulatory compounds in paragraph 0065 does not represent compounds that modulate integrins or integrin receptors. Applicant states that the compounds listed in paragraph 0065 can be used in combination with the modulatory compounds. Applicant argues that support for the changes are found in the previous paragraph (0064) that refers to modulatory compounds, and states that such compounds can be used individually or in a cocktail containing more than one compound. These are not persuasive.

Applicant has not provided evidence that the specification ever contemplated the use of modulatory compounds in conjunction with non-modulatory compounds. Presently amended paragraph 0065 clearly has changed the disclosure such that a new concept is disclosed as part of the invention; the use of modulatory and non-modulatory compounds together. The specification is to clearly set forth applicant's invention at the time of filing. Applicant cannot amend the specification because of errors found post-filing unless they can provide evidence. In reading paragraph 0065 as originally filed, perhaps the artisan would have believed applicant had found that the list of compounds in paragraph 0065, previously thought not to modulate integrin or integrin receptor activity, had, by applicant, now been shown to have such activity. Further, β-amyloid contains an RHD sequence which is the integrin recognition site in Aβ (Matter, page 1019, col. 1, parag. 2, lines 4-6) and this sequence is similar to the RGD sequence that is the integrin recognition site in many

extracellular proteins (Matter, page 1019, parag. 2, lines 6-9). The RGD sequence is disclosed in paragraph 0064 as a modulator of integrin or integrin receptors. Clearly, the artisan reading the original specification could have accepted the concept that β-amyloid had modulator activity. Additionally, in neither paragraph 0064 nor paragraph 0065 is there any description of other the "combination of more than one compound" in any cocktail. Thus, this passage does not support the amendment of paragraph 0065 to change "modulatory compounds" to "compounds that maybe used with modulatory compounds." From a reading of the entire specification, the use of modulatory and non-modulatory compounds together in a cocktail is not contemplated in the specification at the time of filing. As new contemplations of the invention are not permitted entry, the amendment to paragraph 0065 as filed, is new matter. Applicant might consider filing a CIP to correct the error. However, the CIP application would not be given benefit of priority to the present filing date, nor the filing date of the provisional application.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 79 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The examiner cannot find support for claim 79 in the specification, and applicant has not pointed to where such support can be found. Applicant should provide evidence of specification support for amendments to the claims.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7, 8, 13, 16-18, 37, 59-61, 63, 64, 69 and 72-74 remain rejected under 35 U.S.C. 102(b) as being clearly anticipated by Harris-White et al (1998) The Journal of Neurosci. 18, pp. 10366-10374.

Harris-White teaches wild-type rat hippocampal slices as an in vitro model for β-amyloid deposition (page 10368, col.1, parag. 1, lines 1-3). In particular Harris-White teaches determining the effect of TGFβ on β-amyloid using the hippocampal slice model where the hippocampal slice is incubated simultaneously in media comprising both TGFβ and β/A (page 10368, col. 2, parag. 1, lines 1-3). Harris-White teaches that isoforms of TGFβ added to hippocampal slice cultures in conjunction with the addition of Aβ resulted in an increase in the amount of A/β within the slice and a 2 to 3-fold increase of control experiments in the number of plaque-like deposits and prolonged the course of cellular Aβ staining (page 10368, col. 2, parag. 4, lines 5-7 and page 10369, col. 2, parag. 1, lines 22-25). Harris teaches detection of the increase in Aβ deposition, that is Aβ sequestration, uptake and accumulation, in hippocampal brain slices with antibodies to regions of the Aβ1-40 polypeptide by both imaging and ELISA (page 10367, col. 1, parag. 5, lines 1-5). Thus, Harris-White clearly anticipates the claimed invention.

Applicant argues that the amendment to paragraph 0065 (specification, page 19) that A/β is not a condition that modulates integrins or integrin receptors, that Harris-White use of either A/β or TGFβ failed to meet one of the limitations of the claimed inventions. Applicant also argues that the examiner has not pointed out the manner in which the cited

art teaches the additional limitations of the claimed methods. These arguments are not persuasive.

The art at the time of filing taught that A/β binds to integrins. β1 integrins have been shown to mediate cell adhesion to the Aβ protein, and α5β1 integrin has been proposed to be the integrin responsible for the binding (Matter, page 1019, col.1, parag. 2, lines 1-4); β-amyloid contains an RHD sequence which is the integrin recognition site in Aβ (Matter, page 1019, col. 1, parag. 2, lines 4-6); and this sequence is similar to the RGD sequence that is the integrin recognition site in many extracellular proteins (Matter, page 1019, parag. 2, lines 6-9). Binding of Aβ certainly is a modulator of integrin as taught by Harris-White. The specification states "[t]he present invention is based on, in part, the discovery that integrins and/or integrin receptors can modulate the sequestration and/or accumulation and/or uptake of Aβ in cultured brain cells." Harris-White, as indicated in the rejection above, teaches an increased amount of A/β in hippocampal slices. This increased mount of A/β is an increase in uptake or sequestration of the peptide.

The examiner does not find any limitations to the claims included in this rejection that are not pointed out in the rejection.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5, 6, 36 and 59-62 remain rejected under 35 U.S.C. 103 (a) as being unpatentable over Matter et al (1998) Journal of Cell Biology 141, pp. 1019-1030 in view of Harris-White et al (1998) The Journal of Neurosci. 18, pp. 10366-10374.

Matter teaches that integrin α5-negative neuroblastoma cells, IMR-324β1, transformed with DNA sequences encoding integrin α5, when incubated with Aβ, resulted in a 5-fold decreased accumulation of Aβ deposits in the cells as compared to non-transformed control cultures (1024, col. 1, parag. 1, lines 4-6).

Harris-White teaches wild-type rat hippocampal slices as an in vitro model for β-amyloid deposition (page 10368, col.1, parag. 1, lines 1-3). Harris teaches detection of Aβ deposition, that is Aβ sequestration, uptake and accumulation, in hippocampal brain slices (page 10367, col. 1, parag. 5, lines 1-5). Harris-White offer motivation in stating the hippocampal slice model permits conditions most similar to the in vivo situation that also allow for a longer time course for the development of neurotoxicity (page 10369, col. 2, parag. 1, lines 11-14).

Therefore, it would have been obvious to the ordinary artisan at the time of the instant invention, to perform the analysis of Matter et al using the hippocampal brain slice assay of Harris-White given the motivation of Harris-White that the brain slice assay is more reflective of the in vivo situation than cultured cells.

Applicant argues that the use assumption of Aβ as a modulator of integrin is incorrect as argued in response to the 102 rejections. In response, the examiner refers applicant to the rebuttal of those arguments above.

Applicant argues that Harris-White and Matter do no more than observe cells or tissues and do not determine the effect of a substance on characteristics of neurodegenerative diseases. This argument is not persuasive.

Claim 1 states "[a] method for determining the effect of a substance on sequestration, uptake or accumulation of amyloid in brain cells. The substance in Matter is be the DNA sequence encoding integrin α5.

Claims 1, 13-15, 59 and 69-71 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Matter et al (1998) Journal of Cell Biology 141, pp. 1019-1030 in view of Harris-White et al (1998) The Journal of Neurosci. 18, pp. 10366-10374.

Matter teaches the deposition returned to control levels in the presence of an anti-α5 antibody (page 1024, col. 1, parag. 1, lines 4-6). Matter further teaches the peptide RGD and GRGDSP inhibited Aβ binding to the cell (page 1023, col.1, parag. 1, lines 23-33).

Harris-White teaches wild-type rat hippocampal slices as an in vitro model for β-amyloid deposition (page 10368, col.1, parag. 1, lines 1-3). Harris teaches detection of Aβ deposition, that is Aβ sequestration, uptake and accumulation, in hippocampal brain slices with antibodies to regions of the Aβ1-40 polypeptide by both imaging and ELISA (page 10367, col. 1, parag. 5, lines 1-5). Harris-White offer motivation in stating the hippocampal slice model permits conditions most similar to the in vivo situation that also allow for a longer time course for the development of neurotoxicity (page 10369, col. 2, parag. 1, lines 11-14).

Therefore, it would have been obvious to the ordinary artisan at the time of the instant invention, to perform the antibody and peptide studies described in Matter using the hippocampal brain slice model of Harris-White given the motivation of Harris-White that the brain slice model is reflective of the in vivo situation than cultured cells.

Applicant argues that Matter teaches no more than the observation that Aβ when added to cultures affects the amyloid matrix in cells. Applicant argues that the conditions set forth in Matter are not the same as "exposing brain cells to a condition that modulates integrins." Applicant argues that regardless of the decrease in Aβ uptake shown in Matter when Aβ antibody or GRGDSP is added to culture, Matter does not teach applicant's method. Applicant states that the examiner may not take disparate observations for different pieces of art in order to make a rejection. These arguments are not persuasive.

Applicant has not provided any reasoning behind their arguments. The examiner maintains that matter in view of Harris-White teaches applicant's claimed invention, in that a decrease in Aβ sequestration/uptake/accumulation is observed. Applicant has not explained why Matter and Harris-White are disparate observation? The subject matter of both references is directed to integrin mediated uptake of Aβ under various culture conditions that modulate integrin activity through the use of substances added to the culture.

Claims 1, 19, 59 and 75 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hass et al (1998) Journal of Biolog. Chem. 273, pp. 13892-13897 in view of Harris-White et al (1998) The Journal of Neurosci. 18, pp. 10366-10374.

Hass teaches the expression of ApoE isoforms in combination with either an APP7562 haloprotein or an APP truncation lacking the Aβ sequence in COS (page a13896, col. 1, parag. 2, lines 1-6). The results of these studies demonstrate binding of ApoE to the N-terminus of APP (page 13897, bridg. parag.).

Harris-White teaches wild-type rat hippocampal slices as an in vitro model for β-amyloid deposition (page 10368, col.1, parag. 1, lines 1-3). Harris teaches detection of Aβ deposition, that is Aβ sequestration, uptake and accumulation, in hippocampal brain slices with antibodies to regions of the Aβ1-40 polypeptide by both imaging and ELISA (page 10367, col. 1, parag. 5, lines 1-5). Harris-White offer motivation in stating the hippocampal slice model permits conditions most similar to the in vivo situation that also allow for a longer time course for the development of neurotoxicity (page 10369, col. 2, parag. 1, lines 11-14).

Therefore, it would have been obvious to the ordinary artisan at the time of the instant invention, to perform the apoE studies described in Hass using the hippocampal

brain slice model of Harris-White given the motivation of Harris-White that the brain slice model is reflective of the in vivo situation than cultured cells.

Applicant argues that there is no motivation to combine Hass with Harris-White to arrive at the claimed invention. Applicant argues that Hass is looking at the APOE gene locus in a cell line and there is no suggestion to apply this observation to brain cells. Applicant argues that even if the model of Harris-White permits a longer time course to develop neurotoxicity, there is still no motivation to combine with Hass, or to determine the effect of a substance on brain cells. These arguments are not persuasive.

Hass is not just looking at APOE gene locus. Hass is determining the effect of two substances, APP7562 haloprotein or APP truncated form, on Apo E binding to APP. Harris-White teaches the hippocampal slice model to determine neurotoxic effect of Aβ. Thus, the artisan would have had motivation to determine the effect of APP7562 and APP truncated forms on Aβ sequestration/uptake/accumulation in hippocampal slices.

With regards to applicant's arguments that the amendment to the specification eliminates Aβ as a modulator of integrins, applicant is referred to the examiner's response above.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant

to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

September 5, 2004